Electronic BANDOLIER

Not everyone has access to the Internet, but increasingly we will be dependent upon electronic rather than paper sources of information. The reason is simple - there will be more of it, it will be easier to access, and it will be up-to-date. Let's face it, even if we have the most recent edition of some whizzo textbook, the chances are that the articles were written two years ago. Two years hence, and long before the next edition is available, the information will be antediluvian.

More & faster

In *Bandolier* on the Internet, we hope to try to gather together large amounts of content (a commodity in short supply in most Internet health sites).

Bandolier's webmaster is concerned about download times - some techno-speak for how fast it takes information to appear on your computer. *Bandolier* pages are designed and monitored so that they should take no more than 10 seconds on the slowest modem. Any more than that and it's your computer or telecom, or the sheer volume of traffic that is slowing things down (and we are pretty sure the slowdown is not at our end).

The *Bandolier* home page - what you get by dialling the address shown below - is shown here. The site won the award for the best NHS website of 1999.

Electronic to paper

On the home page you will find on the left a back issue and subject index, a direct link to *ImpAct*, a link to a NNT calculation sheet, and *Bandolier*'s Internet publications. On the right you find the contents of the current issue. *Bandolier* is also available now in Spanish (as *Bandolera*) since issue 65. There is also the Knowledge Bazaar, a search engine for the whole site, and the Oxford Pain Internet Site.

New from this month on the bottom left is a link to a page (see below) which allows you to download onto your computer a PDF file of every *Bandolier* and *ImpAct* ever produced. All you need is a copy of Acrobat 3.1 (free of charge, and instructions on how to get and do it). Then you can have any issue of *Bandolier* printed out on your desk whenever you want or need it.

Bandolier is produced exclusively on Apple equipment, which is apparently Millennium bug-free, or at least until the year 46,000 or so. So if you have any problems with accessing electronic *Bandolier* in the new year, it is your problem, not ours.

Bandolier PDF Downloads

Year	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
1994		1	2	3	4	5	6		7	8	9	10
1995	11	12	13	14	15	16	17	18	19	20	21	22
1996	23	24	25	26	27	28	29	30	31	32	33	34
1997	35	36	37	38	39	40	41	42	43	44	45	46
1998	47	48	49	50	51	52	53	54	55	56	57	58
1999	59	60	61	62	63	64	65	66	67	68	69	

Simply click on the issue you want and the pdf should magically arrive on your machine. If you are struggling with pdf files look here.

ImpAct PDF Downloads

Year	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
1999					1		2		3		4	

In this issue

The views expressed in **Bandolier** *are those of the authors, and are not necessarily those of the NHSE*

Oxford Pain Internet Site: www.jr2.ox.ac.uk/Bandolier/painpag/index.html

ANTITHROMBOLYTICS AND STROKE IN AF

Atrial fibrillation (AF) is a common dysrhythmia, affecting 2-5% of the general population over the age of 60, but as many as 14% in the over-80s. It affects about 15% of all stroke patients and about 2-8% of patients with transient ischaemic attack. The risk of stroke is high in people with AF - said to be 2-5% per year. AF is often aggressively treated with anticoagulants or antiplatelets - usually warfarin or aspirin respectively - with the aim of reducing stroke and mortality.

An authoritative meta-analysis [1] looks at the efficacy of these treatments. Although our prejudice is that they are effective, having this confirmed, and being able to quantify benefits and risks, is comforting.

Search

A comprehensive strategy looked for randomised trials for nonvalvular atrial fibrillation. Trials looking at prosthetic valves or mitral stenosis were not considered. Blind and non-blinded trials were included, as were studies of primary and secondary prevention.

Outcomes

Because ischaemic and haemorrhagic strokes were not reliably distinguished in many of the trials, 'all strokes' was used as the main outcome. The number of intracranial and extracranial bleeds, and all-cause mortality data was also collected.

Adjusted-dose warfarin versus placebo

There were six trials with 2900 patients and 186 strokes. The mean duration was 1.6 years, the mean INR achieved was 2.0 to 2.9, the mean age was 69 years and 20% had a previous stroke or transient ischaemic attack. The rate of stroke on placebo was 4.6% per year for those with no previous stroke, and 12% a year for those patients who had had a previous stroke.

Benefit

There was an overall reduction in strokes of 60%, from a rate of 5.8% per year with placebo to 2.3% a year with adjusted-dose warfarin. The NNT was 18 (14 to 27). This means that 18 patients have to be treated with adjusted-dose warfarin for 1.6 years to prevent one stroke that would have occurred without treatment. The review [1] quotes one-year NNTs to prevent one stroke of 37 for primary prevention and 12 for secondary prevention for adjusted dose warfarin compared with placebo.

All-cause mortality was decreased by 1.6% a year in patients receiving warfarin.

Harm

There were six intracranial haemorrhages in 1450 patients receiving warfarin (annual rate 0.3%) and three in 1450 with placebo (annual rate 0.1%). The annual rate of major extracranial haemorrhage was 0.6% for placebo, with a relative risk of 2.4 (1.2 to 4.6) for warfarin.

Aspirin versus placebo

There were six trials with 3225 patients and 349 strokes. The mean duration was 1.5 years, the daily aspirin dose was 325 mg/day or below in all but 21 patients, the mean age was 70 years and 40% had a previous stroke or transient ischaemic attack. The rate of stroke on placebo was 5.2% per year for those with no previous stroke, and 13% a year for those patients who had had a previous stroke.

Benefit

There was an overall reduction in strokes of 20%, from a rate of 7.9% per year with placebo to 6.5% a year with aspirin. The NNT was 48 (23 to >1000). This means that 48 patients have to be treated with aspirin for 1.5 years to prevent one stroke that would have occurred without treatment. The review [1] quotes one-year NNTs to prevent one stroke of 67 for primary prevention and 40 for secondary prevention for aspirin compared with placebo.

All-cause mortality was not significantly reduced by aspirin.

Table 1: Results of randomised trials of antithrombotic interventions to prevent all-cause stroke in atrial fibrillation

Strokes on:								
Warfarin		Aspirin		Placebo				
Number	Percent per year	Number	Percent per year	Number	Percent per year	Duration (years)	Relative risk (95%CI)	NNT (95%CI)
53/1450	2.3			133/1450	5.8	1.6	0.4 (0.3 to 0.6)	18 (14 to 27)
		159/1624	6.5	190/1601	7.9	1.5	0.8 (0.7 to 0.98)	48 (23 to >1000)
82/1416	2.6	123/1421	4			2.2	0.7 (0.5 to 0.9)	35 (21 to 104)

Table 2: Modelling benefit and harm for antithrombotic therapy for all-cause stroke in atrial fibrillation

Modelling events in 1000 patients with non-valvular atrial fibrillation: benefits and harms with antithrombotic treatment

| | All strokes | | | | Major extracranial bleed |
| | Primary prevention risk: | | | Secondary prevention | |
Events per year with:	Low	Moderate	High		
No therapy	10	35	60	120	6
Adjusted-dose warfarin	4	14	24	48	9
Aspirin (low dose)	8	28	48	96	7

Illustration of the magnitude of treatment in one year effects from clinical trials, assuming different initial risk rates, and based on 1000 patients who have not had a stroke and with low moderate and high risk of stroke, and for 1000 patients who have had a stroke. Shaded area indicates harm from major extracranial bleeds.

Harm

There were four intracranial haemorrhages in patients receiving aspirin (annual rate 0.2%) and three in those with placebo (annual rate 0.1%). The annual rate of major extracranial haemorrhage was 0.5% for aspirin and 0.6% for placebo.

Adjusted-dose warfarin versus aspirin

There were six trials with 2837 patients and 205 strokes. The mean duration was 2.2 years, the mean INR achieved was 2.2 to 3.1, the mean age was 71 years and 21% had a previous stroke or transient ischaemic attack. The rate of stroke on aspirin was 2.7% per year for those with no previous stroke, and 11% a year for those patients who had had a previous stroke.

Benefit

There was an overall reduction in strokes of 35%, from a rate of 4.0% per year with aspirin to 2.6% a year with adjusted-dose warfarin. The NNT was 35 (21 to 104). This means that 35 patients have to be treated with adjusted-dose warfarin for 2.2 years to prevent one stroke that would have occurred with aspirin. The paper quotes one-year NNTs to prevent one stroke of 167 for primary prevention and 14 for secondary prevention for warfarin compared to aspirin, but with some data excluded for this calculation.

All-cause mortality was similar for both treatments.

Harm

There were 17 intracranial haemorrhages in patients receiving warfarin (annual rate 0.5%) and seven in those with aspirin (annual rate 0.2%). The annual rate of major extracranial haemorrhage was 0.2% for higher for warfarin compared with aspirin, a relative risk of 2.0 (1.2 to 3.4).

Comment

This is a review written by people involved in some of the main trials in this area, and with a view to examining benefit and harm. The reviews will also be available separately on the Cochrane Library in early 2000.

The authors modelled the effects of treatment - the benefit in terms of reductions in all-cause strokes, and the harm in terms of major extracranial bleeds. The effects based on cohorts of 1000 patients over one year, at various baseline risk of stroke and for primary and secondary prevention are shown in Table 2. Benefit outweighs harm.

Given that atrial fibrillation is often aggressively treated in primary care, and is relatively common (three million warfarin prescriptions in primary care in England in 1998), this conclusion is comforting. The review did not deal with people with structural heart disease, in whom the risk of stroke may be higher. It is a worthwhile read.

Reference:
1   RG Hart, O Benavente, R McBride, LA Pearce. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. Annals of Internal Medicine 1999 131: 492-501.

PAIN - THERE'S A LOT OF IT ABOUT

Bandolier is keen to know what's common. A superb study of chronic pain in the community [1] gives a bottom line answer that half of us suffer from chronic pain of some sort.
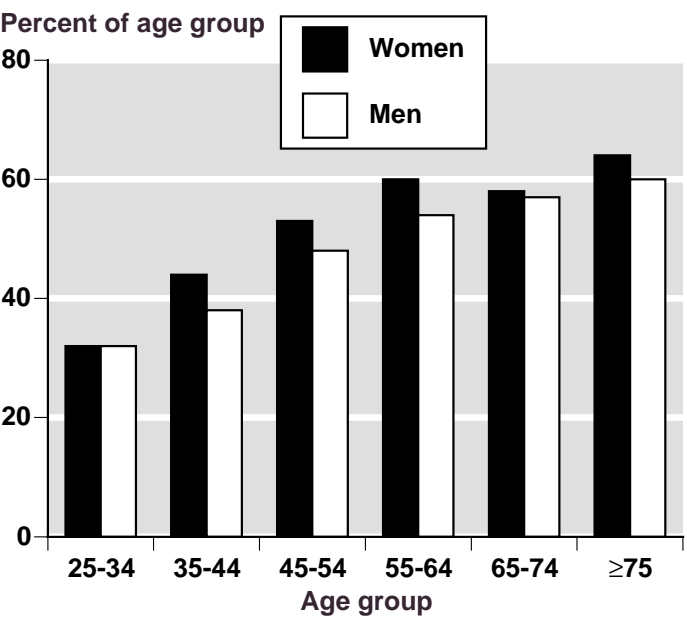
Survey

The study was done in the Grampian region of Scotland. There were just under 400,000 people in general practices which use the General Practice Administrative System for Scotland (GPASS), a common electronic data handling system that many believe is the best developed in the UK. Practices were invited to participate and about half did, and these covered about a third of the Grampian population. About 5000 questionnaires were sent to people from the practices, of which 4,400 were delivered and 3605 (four out of five) replied.

The definition of chronic pain used was "pain or discomfort, that persisted continuously or intermittently for longer than three months". The questionnaire was piloted and validated.

How many people have chronic pain?

Half of the respondents reported having chronic pain. This increased with age in women and men from about one-third of those aged 25-34 to almost two-thirds in those older than 65 years (Figure 1). Chronic pain is associated with older age, living in rented council accommodation, being retired or being unable to work.

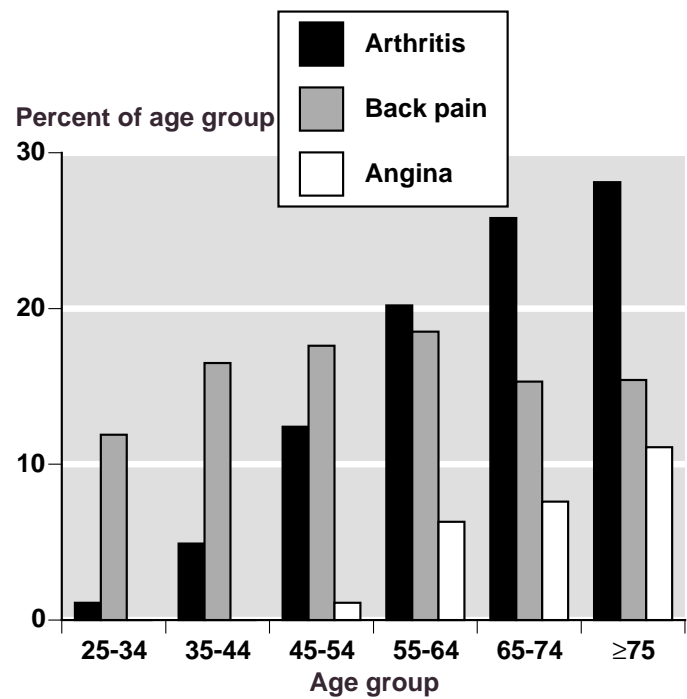## Figure 1: Reported chronic pain by age and sex

What pains and when?

The two most common reasons for chronic pain were back pain, which varied little with age, and arthritis, which rose dramatically with age to afflict a quarter of people in their

60s or older (Figure 2). Angina was also more common in older age groups (Figure 2). Women's problems were more common (5-8%) in the age range 25-54 years than at older ages. Pain from injury and unknown causes was constant with age at about 4.5%.

Figure 2: Type of chronic pain by age

How bad was the pain?

The severity of chronic pain was measured using questions relating to the persistence and severity of the pain and the disability it caused. Patients were then classified into five grades, with grade 0 being pain free. The definitions used to grade the pain, and the proportion of people affected are shown in the Table. A quarter of people with chronic pain had pain that was highly disabling and at least moderately limiting. A further quarter had pain that was of high intensity.

Table: Grade of pain severity in people who reported having chronic pain

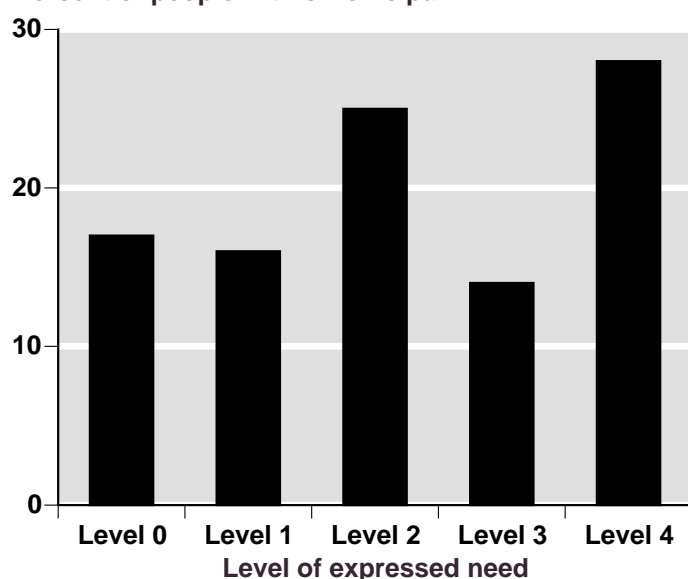| Pain grade	Description	Percent of people with chronic pain
Grade 1:	low disability/ low intensity	49
Grade 2:	low disability/ high intensity	24
Grade 3:	high disability/ moderately limiting	11
Grade 4:	high disability/ severely limiting	16

How much help do people need?

This was measured using four questions to try and assess demand for and uptake of health service resources.

♦ Have you sought treatment for your pain or discomfort recently?
♦ Have you sought treatment for your pain or discomfort often?
♦ Have you taken painkillers for your pain or discomfort recently?
♦ Have you taken painkillers for your pain or discomfort often?

Five levels of expressed need were determined from the number of positive responses to these questions, from level 0 (no expressed need; answered no to all four questions) to level 4 (high expressed need; answered yes to all four questions). The level of expressed need is shown in Figure 3. Higher levels of expressed need were more frequent.

Figure 3: Expressed need in people with chronic pain

Percent of people with chronic pain

Comment

The merits of this study are that it is large, it uses pain definitions based on that of the International Association for the Study of Pain, and for most *Bandolier* readers, is British. It shows that about half of people in the community suffer chronic pain, and that for about half of those the pain is significant. The indications are that much of the pain is poorly treated and that there is a potentially large demand for more or better pain relief services for the community.

This is sobering stuff, because understandably much of the demand will be in older people, and we are set to have lots more older people in coming decades.

Reference:

1   AM Elliott et al. The epidemiology of chronic pain in the community. Lancet 1999 354: 1248-52.

ORAL ZINC AND LEG ULCERS

Leg ulcers are a big problem because they are common at about 1-2 per 1000 people, but more common in the elderly. They are often slow to heal, and are disabling for those who have them, reducing mobility, independence and quality of life. A systematic review sought evidence of benefits to healing of oral zinc from randomised trials [1].

The searching strategy was heroic, but found only six small randomised studies. Five were in venous ulcers and one in arterial ulcers. Oral zinc was given at doses of 440-660 mg daily, mainly compared with placebo, and the studies were over periods from four weeks to 14 months. The predominant outcome used was number of ulcers healed.

In four trials of oral zinc compared with placebo over three to ten months, 33/65 (51%) of venous ulcers were healed compared with 33/76 (43%) with placebo (Figure). This was not statistically significant, with a relative benefit of 1.2 (95% confidence interval 0.9 to 1.7).
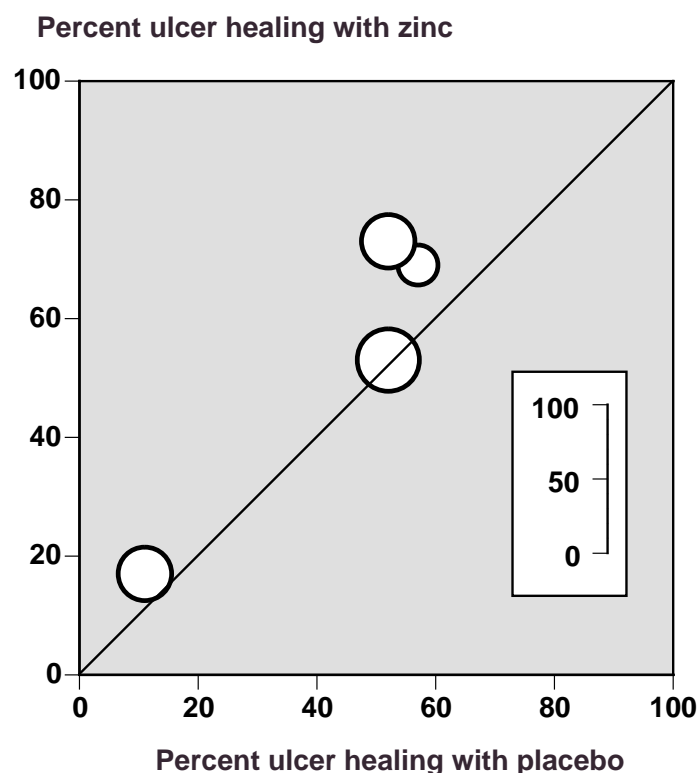
Comment

Clearly there is not a huge amount of information on which to base a judgement. However, it is highly unlikely that any massive benefit of oral zinc for healing of leg ulcers is being missed.

Reference:
1   EA Wilkinson, CI Hawke. Does oral zinc aid the healing of chronic leg ulcers? Archives of Dermatology 1998 134: 1556-60.

Figure: Four trials comparing oral zinc with placebo for healing of venous leg ulcers

Percent ulcer healing with zinc

Percent ulcer healing with placebo

Diagnostic testing emerging from the gloom?

Bandolier has long sought good evidence about diagnostic tests. We want to know how well a particular test or diagnostic algorithm works in a particular setting. We want to have confidence that we can reliably predict that a patient has a high chance of having or not having a disease. Our subsequent decisions about treating, not treating, or referring depend on the adequacy of our diagnosis.

The problem is that there is little evidence to be found at all, and little of that is good news. A succession of stories saying that tests are useless loses impact. Without empirical evidence of bias in study architecture, we are rudderless in the midst of a tidal surge.

Nil desperandum. Help is at hand. Two recent publications have begun to lay a little more foundation and to provide a sea-anchor in this turbulent area.

CARE essay

In *Bandolier* 66 we featured the CARE project (Clinical Assessment of the Reliability of the Examination), a collaborative study of the accuracy and precision of the clinical examination. The Internet address is http://www.carestudy.com/.

The main plotters behind CARE, Finlay McAlister, Sharon Straus and David Sackett have written a terrific essay on the need for large prospective studies of the clinical examination [1]. This is an important, perhaps seminal paper. More than any other *Bandolier* has read it explains why new research, indeed, new thinking, is required. It's beautifully written and easy to follow, and is essential reading.

Their prime example is chronic obstructive airways disease (COAD). A systematic review sought physical signs for differentiating patients for those with COAD from those with normal pulmonary function. There were many, but no one sign was found in more than a third of studies.

For each of the the four most commonly used physical signs the range of diagnostic accuracy from the literature was huge. Positive likelihood ratios spanned the range from about 1 to over 10: from useless to highly predictive.

They also examined the quantity and quality of evidence from systematic reviews for a variety of signs for different conditions. There were few high-quality studies, and those there were were small.

The bottom line is that at best we have hand-me-down evidence, and experience. We have little or no objective proof of the quality of diagnostic accuracy of clinical examinations.

Levels of evidence

One description of levels of evidence commonly used is

Level	Criteria
Levels of evidence for studies of diagnostic methods	
1	An independent, masked comparison with reference standard among an appropriate population of consecutive patients.
2	An independent, masked comparison with reference standard among non-consecutive patients or confined to a narrow population of study patients.
3	An independent, masked comparison with an appropriate population of patients, but reference standard not applied to all study patients
4	Reference standard not applied independently or masked
5	Expert opinion with no explicit critical appraisal, based on physiology, bench research, or first principles.

shown in the box. The keys to good quality are independence, masked comparison with a reference standard, and consecutive patients from an appropriate population. Lower quality comes from inappropriate populations and comparisons that are not masked or with different reference standards. Other standards have been applied to diagnostic tests, as reported in *Bandolier* 26.

Bias in diagnostic test studies

What we have lacked up to now is proof that poor study design is associated with bias. A new contribution from Holland [2] provides the missing link.

It searched for and found 26 systematic reviews of diagnostic tests with at least five included studies. Only 11 could be used in their analysis, because 15 were either not systematic in their searching or did not report any sensitivity or specificity. Data from the remainder were subjected to mathematical analysis, to investigate whether the presence or absence of some item of proposed study quality made a difference to the perceived value of the test.

There were 218 studies, only 15 of which satisfied all eight criteria of quality for the analysis. Thirty percent fulfilled at least six of eight criteria. The relative diagnostic odds ratio used indicated the diagnostic performance of a test in studies failing to satisfy the methodological criterion relative to its performance in studies with the corresponding feature. Over-estimation of effectiveness (positive bias) of a diagnostic test was shown by a lower confidence interval for the relative diagnostic odds ratio of more than 1.

The results are shown in the Table. Use of different reference tests, lack of blinding and lack of a description of either the test or the population in which it was studied led to positive bias. But the largest factor leading to positive bias was evaluating a test in a group of patients already

Table: Estimates of bias in study architectures for diagnostic tests

Study characteristic	Relative diagnostic odds ratio (95% CI)	Description
Case-control	3.0 (2.0 to 4.5)	A group of patients already known to have the disease compared with a separate group of normal patients
Different reference tests	2.2 (1.5 to 3.3)	Different reference tests used for patients with and without the disease
Not blinded	1.3 (1.0 to 1.9)	Interpretation of test and reference is not blinded to outcomes
No description test	1.7 (1.1 to 1.7)	Test not properly described
No description of population	1.4 (1.1 to 1.7)	Population under investigation not properly described
No description reference	0.7 (0.6 to 0.9)	Reference standard not properly described

The relative diagnostic odds ratio indicates the diagnostic performance of a test in studies failing to satisfy the methodological criterion relative to its performance in studies with the corresponding feature.

known to have the disease and a separate group of normal patients - called a case-control study here.

Comment

The amount of positive bias in poorly conducted studies of diagnostic tests is extremely worrying. Most information for most laboratory tests is only available in the form of case-control studies - those with the highest bias.

Take one example, that of the fashionable free-PSA test [3]. The likelihood ratios from the early studies were 2 to 7. This might be useful in a population of men referred to a urology clinic with prostate cancer or BPH, but most of the studies were case-control studies. If the likelihood ratios were biased, and in truth were lower, the test may be of no use even in a high prevalence setting.

It is all very worrying. It is time someone in academe, or the NHS, or industry sat up and took notice. The problem is not just, or even, with treatment. The problem is knowing who is to be treated. The message is that we need to get back to first principles and do some large high-quality real-life studies. CARE has started that for the clinical examination, but there's absolutely no reason why similar studies could not be performed in other setting for laboratory tests and clinical examinations combined.

References:
1   FA McAlister, SE Straus, DL Sackett. Why we need large, simple studies of the clinical examination: the problem and a proposed solution. Lancet 1999 354: 1721-24.
2   JG Lijmer et al. Empirical evidence of design-related bias in studies of diagnostic tests. JAMA 1999 282: 1061-6.
3   RA Moore. Free PSA as a percentage of the total: where do we go from here? Clinical Chemistry 1997 43: 1561-2.

GENETICS WEBSITE

Getting good, readable and up-to-the minute information about genetics and disease is difficult for all of us. Something written for anyone to understand is a treasure. *Bandolier* recommends the public health genetics site in Cambridge, with good information on the following:

- Alzheimer's disease
- Breast/ovarian cancer
- Colorectal cancer
- Cystic fibrosis
- Down's syndrome
- Fragile X syndrome
- Hereditary haemochromatosis
- Thrombophilia and Leiden Factor V

The address is: http://www.medinfo.cam.ac.uk/phgu/

The disease database can be found by entering the information database and then disease profiles. But this site is packed with useful information, and should be bookmarked on your browser.

Fallacies in health

There are truths, universal truths, and universal truths which have proved to be neither universal nor true. *An ageing population will lead to much increased healthcare costs.* Everyone uses it all the time, as a prop, or excuse, or an opportunity. But is it *true*?

Not according to Charles Normand, professor of health policy at the London School of Hygiene and Tropical Medicine. He has written [1] a lovely analysis of ten popular health economic fallacies. This is a paper worth having close to hand, because if you study it, it has clues on how to debunk other universal truths when someone uses one as an alternative to thinking.

Here are just some of the fallacies, with a short explanation of why they are fallacies:

Advances in technology increase health costs

Why should they? Advances in technology can only, in themselves, lower costs. If something does the same job at a lower cost, then the lower cost will win, whether it is advanced or not. An example from some years ago when monoclonal antibodies were in vogue was the thyroxine test which cost £1 a test for a monoclonal test, versus 5p a test for standard antibody. But they gave the same result. So collapse of new test (or its price).

The problem is that new technology often does similar, but not the same, job. New technology may increase quality, or efficiency, or we believe that it does. But measuring these things is difficult, so technology creeps in without really being evaluated in terms of bangs per buck.

Ageing populations will lead to increased costs

But elderly people are healthier now, healthcare costs are more related to approaching death than just age, and ageing is itself supplying more informal carers who are fit and able to help.

Buildings are expensive

The cost of new health service facilities (including equipment) is 50% to 200% of the annual running costs. So if buildings last 40-100 years, they are cheap.

Governments cannot afford more money for health services

Rising health service spending should be expected in a modern economy. This is because making things is cheaper and easier with automation, and because healthcare is people-led not thing-led. So a rise should be expected, especially as more affluence demands better health to enjoy that affluence. The problem with public spending is tax, because those affluent people also want more of their income to spend.

Better health services get people back to work, and so are cheaper

There are many reasons why this is wrong, as many GPs and others recognise. To cut to the chase, relationships between health services and the ability to work are slight, at best.

Focusing on the major diseases makes sense

No it doesn't. The issue is the size of the solution and not the size of the problem. Many common, chronic diseases have therapies that are at best only palliative. Solutions which are effective (cures) are those which should be sought. So arthritis of the hip may be more important than heart disease, ranked by cost-effectiveness.

These are just a few short précis of a fascinating and enjoyable read. Particularly worth reading was the acknowledgements, where Normand thanks the many university and health services colleagues who keep repeating these fallacies.

Reference:
1   C Normand. Ten popular health economic fallacies. Journal of Public Health Medicine 1998 20: 129-132.

Bandolier Conference on Stroke:

what to do second - optimising secondary prevention and follow-up care programme

Reminder that this conference is on Thursday December 16 at the Stopford Room, University of Manchester. The cost to NHS or university folk is £100, and for the private sector £250. A small number of reduced price places will be available for students. Fax Eileen Neail on 01865 226978, or call on 01865 226132 for some places still available.